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13. SUPPLEMENTARY NOTES					
14. There are no significant research findings to report at this time. The VCU Center for Clinical and Translational Research and Technology Services is working to create and review design of media and publications for community notification activities. Standard Operating Procedures (SOP's) are being reviewed and revised as we conduct walk-through scenarios. The plan is to have SOP's formally in place when mock drills take place. Data collection tools are undergoing review by actual users and final touches for this tool are being implemented. Communication is ongoing with DSMB members and Safety Monitor to inform them of progress and plans for trial to begin within the next 4-5 weeks. IRB submission paperwork for approval by the Secretary of the Army and HRPO is being finalized.					
15. SUBJECT TERMS <i>nothing listed</i>					
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Introduction

The contract for our project, Prehospital Use of Plasma for Traumatic Hemorrhage, was awarded June 1, 2012. The greater part of this past year was spent seeking the regulatory approvals required prior to enrolling patients. Approval was granted that allowed for a nurse Project Coordinator under the direct supervision of the PI to oversee completion of the IND and coordinate all facets of the study. The IND was submitted in January 2014 and written approval from the FDA to proceed with the study was received in February 2014. (Appendix 1) With permission to proceed, the FDA suggested a few changes to the IND that were addressed in a follow-up letter. (Appendix 2) Following FDA approval, our next step was to obtain VCUMC IRB approval. The request for VCU IRB approval is submitted and we are currently waiting for written approval from our Internal Review Board and preparing for the Secretary of Army HRPO Approval. The study team is working diligently and will be prepared for study enrollment as soon as all regulatory requirements to proceed are met.

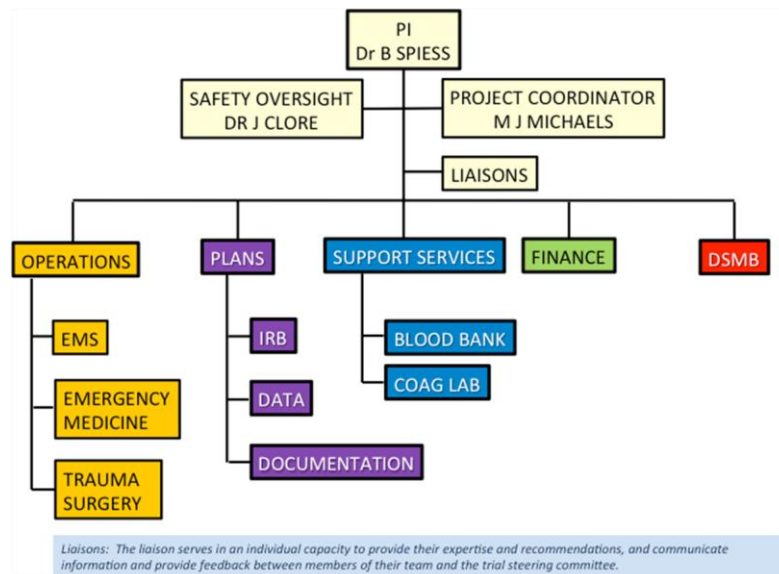
Body

During this reporting period that outlines the past 12 months, several key changes were made to the original study design as recommended and approved by the FDA. These included:

- The primary objective of this study is to compare the 30-day mortality between of TP (Group A thawed plasma products) versus normal saline (NS) infusion at earliest contact administered by trained EMS providers in patients who have sustained severe poly-trauma / major hemorrhage.
- Secondary objectives of this study include: comparing vital signs, lab values such as lactate, total bicarbonate and pH, hemoglobin and hematocrit on arrival at scene, entry to VCU ER, 30 minutes after arrival, 1 hour after arrival and 24 hours after arrival. Coagulation function between these 2 groups will be compared and include fibrinogen, factor V, factor VIII, pT, aPTT, von Willebrand's factor, D-dimer, PFA-100, platelet count, flow cytometry, and lipidome testing (arachidonic acid metabolism, eicosinoids, and prostacyclin expression) at baseline, 30 minutes after arrival, 8 hours after arrival and 24 hours after arrival.
- Rates of multi-system organ failure, renal failure, number of days in the ICU, number of days in the hospital, number of days on a ventilator, number of operations, number of infections, and cumulative utilization of blood products individually will also be compared between these 2 groups.

Plasma will be carried everyday in EMS supervisor vehicles and subjects will be randomized to receive TP or Saline.

Beginning January 2014 a new structure of team reporting and accountability was implemented to facilitate the work that needed to be accomplished in this multi-faceted study. The diagram shown provides a visual of our Team structure. Every aspect of the clinical trial from the moment of subject identification as meeting enrollment criteria to data collection, capture, and evaluation is assigned to a Liaison. The designation of project liaisons is necessary to facilitate coordination and communication between organizational units of the trial, and to achieve the best use and allocation of resources or employment of services of one group by another.



The goal of this structure is to enable trial success by ensuring that the different organizational groups involved in this trial can work together to achieve mutual understanding and unity of effort.

A summary of reports from each Liaison follows:

The PUPTH team **Operations Liaison**, an EMT/PhD researcher, has been instrumental in mapping strategies for patient identification, data collection and task allocation. An annual report summarizing the goals, activities, procedure development and the items to be accomplished follow:

GOALS:

- Safe and adequate delivery, storage, and handover of plasma from Blood bank to EMS and vice-versa
- Seamless and error-free collection of blood samples from patients and delivery to PUPTH personnel
- Seamless and error-free chain of communication between EMS and relevant parties (ED, Blood Bank)

Activities:

- Designed Powerpoint EMS training course in PUPTH protocol. The training course consists of 50 slides, and includes an introduction to the study, training outline, EMS field protocols (patient inclusion and exclusion criteria, study activation protocol, consent protocol, blood sampling, documentation,

risks of plasma administration, protocol for transfusion-related adverse reactions), and contact information

- *Training course distributed to EMS agencies for uploading on protected agency sites.*
- *Established checklist system for EMS patient enrollment, consent, blood sampling, data acquisition*

Procedure development:

- *In collaboration with the Coagulation laboratory, development of blood sampling 'kits'.*
- *Ordered all relevant supplies for sample kits (vacutainers, blood sampling accessories, bags, boxes, labels)*
- *Research, identify, and comparison price barcoding systems to streamlining sample tracking and inventory procedures. Ordered all relevant supplies.*
- *Met with RAA for kit oversight, approval, and refinement*

To Complete:

- *PRIORITY ITEM: Establish contact information channels for EMS providers for PUPTH protocol activation (Liaison with ED, MCV Communication/operations)*
- *Establish contact information channels for Biostatistics for PUPTH data collection, randomization (Liaison with ED, MCV Communications/operations)*

Fine-tuning of the protocols and procedures will occur in several planned “walk through” and “table-top” simulations followed by 2 "mock drills" prior to the first patient enrollment.

The PUPTH team **Plans Liaison** submitted the following summary report:

ITEM: Accomplishments

sub-ITEM: Community Consultations.

Prior to the start of the community consultation phase, the data management team, led by Brian Bush of the Department of Biostatistics, designed and created two sets of scannable paper surveys to match the two different formats of community consultation sessions that were to be conducted.

Subsequently, Biostatistics student research assistants (Amanda E. Gentry and Edmund R. Glass) picked up community consultation surveys from the study coordinator. Using a combination of automated scanning and careful checking by eye, Bush, Gentry, and Glass converted the marks and free text on the surveys into an electronic format that was accessible to statistical methods. The resulting data resided in a password-protected database. Subsequently, Jacob Wegelin summarized these data and produced a detailed report of the survey results. The report consists of 37 pages, including 28 tables and 22 statistical graphics. These thoroughly summarize the community consultation responses. (Appendix 3)

To produce the data summary and report for the community consultations, Jacob A. Wegelin (Department of Biostatistics) wrote approximately 2300 lines of code in the R language for statistical computing. (A small portion of the code was written by student research assistants under Dr. Wegelin's close supervision.)

[Citation: R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL <http://www.R->

[project.org/](#).] As a consequence of Dr. Wegelin's coding, every table, every scalar, every graphic, every date, every cross-reference to a page number or a section number, was generated automatically from the community consultation database.

These custom scripts provided a means by which accuracy of the report could be confirmed and any updates to the database were incorporated into the report, without danger of introducing typographical or copying errors. sub-ITEM: IND resubmission, December 2013 In support of the resubmission of the IND (Investigational New Drug) application to the FDA, Jacob Wegelin composed a new data analysis section. This document provides, in particular, a detailed graphical and verbal explanation of the following: The way in which the methods of Farrington and Manning and of O'Brien and Fleming will be implemented to simultaneously (1) estimate power and sample size, (2) plan and conduct interim tests, and (3) control type one error at 5%. sub-ITEM: Data management for study data Brian Bush, Edmund Glass, and Zachary Martin collaborated with colleagues at the University of Colorado who are conducting the COMBAT study. We studied their information-gathering approach and we implemented shared definitions where feasible, with the goal of supporting future information pooling.

In the PUPTH catchment area, our team initiated meetings with individuals who will gather data for PUPTH, especially EMS and coagulation lab personnel, to facilitate accurate and efficient data gathering.

In addition, we have conducted the first meeting in which we have led the investigators through analysis questions on which the system for data collection will be largely based.

Throughout this process, we are using a continuous improvement methodology to build our study data dictionary. Like our colleagues at the University of Colorado, we are primarily implementing our data collection in the widely accepted web-based REDCap data management system.

ITEM: Reportable outcomes.

As part of the IND resubmission, Dr. Wegelin designed and implemented an innovative graphical illustration of the methods of Farrington and Manning and of O'Brien and Fleming. Although these methods are well known, we are unaware of any previous instance where this kind of graphic has been employed in the illustration of these methods.

Staff of VCU Health System's Blood Bank in collaboration with the PI satisfactorily addressed all questions pertaining to the blood bank that were raised by the FDA after the IND submission (Appendix 4).

The **Support Services Team Liaison** submitted the following report:

The Coagulation Lab is prepared to be staffed 24 hour/day to run study patient lab samples. All instrumentation is in place.

Blood Bank protocols can be found in Appendix 6 of the IND. Staff of VCU Health System's Blood Bank in collaboration with the PI satisfactorily addressed all questions pertaining to the blood bank that were raised by the FDA after the IND submission (Appendix 4).

The refrigerators ordered for the storage of plasma are currently in the VCUMC blood bank undergoing required quality control testing. SOP for stocking and exchange of plasma are in place. The Liaison is currently working on 2 goals: 1. Producing an educational video to be included as part of the required EMS training on the safe handling of plasma, 2. As walk-throughs are carried out,

a continuous evaluation will be ongoing for ways to improve flow / exchange of plasma between blood bank and EMS providers.

Key Research Accomplishments

There are no key research accomplishments to report at this time. We will continue to work with the VCU IRB and then the HRPO for regulatory approvals to continue the study and anticipate that enrollment of patients will begin in July 2014.

Reportable Outcomes

There are no reportable outcomes at this time.

Conclusion

In retrospect, this has been a year full of challenges in addressing the necessary regulatory guidelines prior to initiating such an important clinical study. We are still engaged in the IRB process and anticipate that completion within the next month. EMS training is scheduled, procedures are in place, supplies ordered and mock drills are being planned for. We feel confident that we will be ready for study enrollment as soon as all regulations and requirements are met and permissions received.

Communications and a Meeting were held with a representative from the VCU IRB to review the newest regulatory guidelines issued from the **DOD Protection of Human Subjects and Adherence to Ethical Standards. NUMBER 3216.02**

References

No references at this time.

Appendices

(See Next Page)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

February 28, 2014

Our Reference: IND 15910

Virginia Commonwealth University
Attention: Bruce Spiess, MD
Department of Anesthesiology
Room B1-015B
Sanger Hall
1101 East Marshall Street
PO Box 980695
Richmond, VA 23298

Dear Dr. Spiess:

We have reviewed your investigational new drug application (IND) for Pre-Hospital Use of Plasma for Traumatic Hemorrhage (PUPTH) with exception to informed consent under 21 CFR 50.24 and your study may proceed.

However, we have the following comments:

1. With respect to the protocol:
 - a. Please consider including 24 hour mortality as a secondary endpoint.
 - b. Please add time from EMT arrival at the scene to arrival in the ED in the CRF.
2. With respect to the proposed statistical analysis plan:
 - a. The method stated in Farrington and Manning's paper is for testing the null hypothesis in which the treatment and control groups are assumed to differ in a prescribed magnitude. However, it appears the protocol proposes to test the null hypothesis that the two groups are identical, so that the Farrington and Manning method does not apply. Please clarify the primary hypothesis by including a clear statement of the null and the alternative hypothesis in a mathematical format. Please also revise the protocol so that the proposed hypothesis and testing method are consistent.
 - b. Please provide detailed formula or method on how to calculate the test statistics to be compared to the O'Brien-Fleming stopping thresholds. In addition, we are

unable to verify the thresholds proposed in the protocol (Stage 1: ± 3.49 ; Stage 2: ± 2.46 ; Final: ± 2.00). Please also provide the detail on how you obtained them.

- c. You plan to conduct the first interim analysis for early efficacy with a sample size of 35 subjects per arm. We are concerned that you may not have interpretable results from the analysis due to the small sample size. We recommend that you conduct the first interim analysis for early efficacy at a later stage. In addition, we recommend that the DSMB monitor the safety data more often than three times during the study.
- d. Please provide an explanation/justification for the choice of values used for the sample size calculation: 24% mortality in the saline group and 9.6% in the plasma group.
- e. Please include a missing data section in your protocol. This section should include details regarding how missing data will be handled in statistical analyses, an estimate of the amount of missing data anticipated, and an outline of steps that will be taken in trial conduct to minimize the amount of missing data.
- f. Please define different analysis sets (e.g.: full analysis set based on the intent-to-treat principle, evaluable analysis set, per protocol set) in the protocol, and clearly state which set will be used for the primary and secondary analyses. We recommend that the primary analysis be conducted based on all randomized subjects and sensitivity analysis be conducted on a per protocol treated set.
- g. Please include details on any planned subgroup analyses and how the analyses will be performed. Specifically, please include subgroup analyses by presence or absence of coagulopathy at presentation, injury type, age, race and gender as well as provide p-values as part of the exploratory analysis results.
- h. We recommend developing a detailed statistical analysis plan for the secondary endpoints, including the models to be used and the covariates to be included for each endpoint.
- i. You state that the DSMB may recommend stopping if strong trends exist in secondary efficacy outcomes of the study. We strongly recommend that you do not stop the study early to declare success for efficacy based on the outcomes of the secondary efficacy endpoints.
- j. Please provide in the protocol the details for the DSMB charter, such as the frequency of DSMB meetings. Please refer to the *Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees* for details on how to modify the DSMB charter.

Page 3 – Dr. Spiess

3. With respect to Community Education, on page 47 of the redline strike out version of the protocol submitted on February 25, 2014, please revise the sentence, “The Community Consultation plan-----” to the “Public Disclosure plan -----.”
4. With respect to the Consent Form, Community Consultation and Public Disclosure, please note that your IRB must review and approve any revisions that have been made to the above documents prior to the initiation of the study.
5. With respect to Blood Banking:
 - a. Please clarify how TP with low titers of anti-B will be identified to ensure these products are issued to the ambulances.
 - b. Please clarify whether the transfusion subjects’ blood group will be included in the records so it is available for later review during transfusion reaction investigations.
 - c. Several steps in SOP: PUPTH Study Quality Control Protocols contain the abbreviation “TBD”, e.g., “TBD” appears under Step A2.00 – Reading/Recording Temperatures. Please define the acronym TBD and indicate the specific procedures to be followed when reading the temperatures and when these procedures will be completed, i.e., will the procedures be completed before they are used to train EMS supervisors?
 - d. SOP: Assigning, Issuing, and Returning PUPTH Study Plasma discusses the use of a “bag tag.” Please define “bag tag” and clarify why it will be used when all the information for the tie-tag is already included on the container label.

If you have any questions, please contact the Regulatory Project Manager, Sonday L. Kelly, MS, RAC, at (301) 827-6162.

Sincerely yours,



For
Jay S. Epstein, MD
Director
Office of Blood Research and Review
Center for Biologics
Evaluation and Research



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April 21, 2014

Department of Health and Human Services
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20857

Re: IND #15910, Investigational new drug application for Pre-Hospital Use of Plasma for Traumatic Hemorrhage (PUPTH).

Dear Reviewers:

Thank you for the guidance and feedback you provided with respect to our protocol. With your permission we have proceeded with the next set of requirements for the PUPTH clinical study and are currently awaiting a response from the Internal Review Board at VCUMC before beginning the next phase.

We want to share with you our plan of action to the comments made in the letter dated February 28, 2014.

1. With respect to the protocol:
 - a. We will add 24hour mortality to the list of secondary endpoints for analysis.
 - b. Our data will contain the time of EMT arrival and time of arrival in the ED. Using software, the latter will be subtracted from the former to obtain the elapsed time.
2. With respect to the proposed statistical analysis plan:
 - a. In our revised protocol we will clarify these points
 - b. In our revised protocol we will clarify these points also
 - c. Our sample size and interim analysis are based on our belief that we can enroll about 70 study participants per year. Accordingly, our total planned sample size for three years is 210. We feel that we should perform an interim check about once a year, and consequently the first interim check is scheduled to take place after we have enrolled 35 participants in each arm. The second interim analysis will take place after we have 70 per arm. With regards to monitoring safety

data by the DSMB, our charter for the DSMB for the PUPTH trial strongly recommends at least twice yearly meetings and additional meetings as needed.

ORGANIZATION OF DSMB MEETINGS	
Expected frequency of DSMB meetings	It is recommended that the DSMB meet at least twice yearly and will otherwise depend on the wishes of the DSMB and needs of the trial office will be considered when planning each meeting.
Meeting format	<p>Meetings will be by teleconference, with face-to-face meetings scheduled at the discretion of the DSMB and PI. The PI should try to attend in person if the DSMB requests their presence.</p> <p>Arrangements will be made for an early meeting, before many main outcome measure events have been accrued. This gives a “test run” for the DSMB decision-making process, and a test run for report production.</p>

- d. We will explain in more detail the basis for these two mortality rates.
- e. We will include a missing data section in the revised protocol.
- f. In the revised protocol, we will define the analysis sets.
- g. We plan to include more details on subgroup analyses in the revised protocol.
- h. We plan to add details and specifics on the analysis of secondary endpoints to the protocol.
- i. We agree.
- j. The DSMB charter will be included as an appendix. This is the reference we have used thus far; however, we will review the reference you suggested.

¹ Schultz KF, Altman DG, Moher D, CONSORT group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomized trials. *BMJ* 2010;340:c332doi: 10.1136/bmj.c332; *BMJ* 340: 698-702, 2010

3. With respect to community education, will make the change from Consultation plan...to Public Disclosure plan...as suggested.
4. It is understood that the VCU IRB must approve any revisions to the Consent form, Community Consultation and Public Disclosure forms prior to the initiation of the study.
5. With respect to blood banking:
 - a. Please clarify how TP with low titers of anti-B will be identified to ensure these products are issued to the ambulances.
 - All thawed units will have a titer performed against reagent B-cells to ensure that the titer is not greater than 100. If the units are found to have a titer 100 or greater, they will not be used for the study and additional units will be thawed. Once testing has been completed, these units will be tagged and prepared for issue to the EMT Supervisors when needed.
 - Procedure:

- Heat seal to create a segment from the integral tube attached to the unit (if segments are not already available).
- Remove the plasma from the segment and add to a test tube that is labeled with the unit number from the unit of plasma.
- Mix the contents of the test tube
- Add 1mL of normal saline to a test tube
- Remove 10uL of saline from the test tube (leaving 990uL)
- Remove 10uL of plasma and add to the test tube containing the saline and is labeled with the correct unit number.
- Mix the contents of the test tube
- Add two drops of the diluted plasma to one drop of known reagent B-cells
- Mix
- Spin in centrifuge for 15 seconds
- Read for agglutination macroscopically
- If agglutination is present, the unit will be excluded from use in the study.

b. Please clarify whether the transfusion subjects' blood group will be included in the records so it is available for later review during transfusion reaction investigations.

- All study subjects' blood typing results will be placed in their electronic medical record (Cerner Millennium) upon completion of testing. This information will be available for review by all authorized personnel.

c. Several steps in SOP: PUPTH Study Quality Control Protocols contain the abbreviation "TBD", e.g., "TBD" appears under Step A2.00 - Reading/Recording Temperatures. Please define the acronym TBD and indicate the specific procedures to be followed when reading the temperatures and when these procedures will be completed, i.e., will the procedures be completed before they are used to train EMS supervisors?

- TBD: Is defined as "to be determined"
- The temperature device will meet all FDA regulations and AABB standards for temperature monitoring of blood and blood products. This includes continuous monitoring and recording of the temperature.
- The temperature recording devices will have alarm settings that will sound if the temperature of the plasma storage device comes within 0.5 degrees Celsius of either the low or high temperature settings.
- Temperature indicators, that change color if a unit exceeds the maximum allowable temperature, will also be used alongside the temperature

monitoring devices to ensure all units were continuously maintained at appropriate temperatures.

- All procedures will be finalized once the final temperature-monitoring device has been purchased and validated. Part of the validation procedure is to update the applicable SOPs.
 - All procedures will be completed and approved by the study principal investigator or designee prior to beginning the study.
 - This section must remain TBD until such time the temperature monitoring devices are purchased and all of the manufacturer's instructions can be incorporated into the procedure.
- d. SOP: Assigning, Issuing, and Returning PUPTH Study Plasma discusses the use of a "bag tag." Please define "bag tag" and clarify why it will be used when all the information for the tie-tag is already included on the container label.
- "Bag tag" is the VCU Medical Center term for tie-tag. "Bag tag" and "tie tag" are one in the same and the information contained on each is the same.

If you have any questions, please contact the PUPTH Study Project Coordinator, Mary Jane Michael, RN, MS, at 804-828-5599 or mmichael@vcu.edu

Sincerely yours,

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